Microtubles & Microtubule-associated Proteins

3535-Pos Board B396
Random Hydrolysis Controls Dynamic Instability of Microtubules
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Dynamics of microtubules is fundamental to our understanding of many cellular processes such as chromosome separation, cellular transport and cell motility. One of the most fascinating phenomena related to microtubules is their dynamic instability when the biopolymer molecule can be found in one of two dynamic phases, growing or shrinking. In recent years, there have been significant theoretical and experimental studies of dynamic instability in microtubules. However, mechanisms of this phenomenon are still not well understood. We present a new theoretical approach that allows us to describe dynamic instability using thermodynamically consistent microscopic model. It takes explicitly into account most relevant biochemical transitions, namely, binding of GTP-bound monomers, unbinding of GTP- and GDP- bound monomers, and hydrolysis of GTP-monomers, and it also allows us to have explicit analytical solutions which are very useful for understanding mechanisms. Our model leads to improved comprehensive description of dynamic instability because it not only accounts for the statistics of catastrophes but it also predicts, unlike previous models, the role of rescues in the overall dynamics. Theoretical predictions agree well with available single-molecule experimental observations, and we also suggest many new experiments. Our theoretical analysis is also supported by extensive Monte Carlo computer simulations.

3536-Pos Board B397
A Theoretical Estimation for Dipole Moment Direction of Tubulin Dimer and Assessment of Microtubule Folding Possibility
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Microtubules (MTs) are protein filaments forming a major part of the cytoskeleton of all eukaryotic cells. They are hollow cylinders with an inner radius of 15 nm and outer radius of 25 nm and with a length of up to the cell radius made up of tubulin dimers. There exist various theories about the formation of MTs from tubulin dimers. They mostly agree that MTs grow mainly along the plus-end with the addition of tubulin dimers one by one and in this process the configuration of the polymer is cylindrical. There are also some hypothesis that under specific conditions nucleating tubulin dimers polymerize to form a plain sheet with 13 parallel protofilaments and then the plain sheet folds into a cylinder. In this work we consider such a possibility with calculating the total dipole-dipole interaction energy between all tubulin dimers directly within the plain sheet and in the cylindrical form, MT. This calculation also help us to define a sub space for the direction of the dipole moment of a tubulin dimer in order to allow conformation of a MT.

3537-Pos Board B398
The Width-Length Relationship of Mitotic Spindle in Caenorhabditis Elegans Embryonic Cells: Quantification and Implications for the Regulatory Mechanism
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The mechanisms that regulate the size of supramolecular complexes inside the cell such as the mitotic spindles are mysterious, because the size of these complexes is usually many orders of magnitude greater than that of the constituent macromolecules. For such complexes, some size parameters well correlate with other size parameters, suggesting a mechanism by which the relative size is maintained. The mitotic spindle may be a good model for studying the mechanism underlying the maintenance of the relative size [1]. The mitotic spindle is barrel-shaped molecular machinery critical for accurate chromosome segregation. The regulation of the spindle length, which is the distance between 2 spindle poles, has been well studied. However, little is known about the control of the spindle width, which corresponds to the diameter of the metaphase plate. Previous studies have suggested that the spindle is able to self-organize its shape and thereby maintain a constant aspect ratio between its length and width. In this study, we calculated the widths of metaphase spindles of various sizes that appear during embryogenesis in Caenorhabditis elegans. As expected, the spindle width correlated well with the spindle length; however, the aspect ratio between the length and the width of the spindle was not constant. From the results of our study, we formulated an equation for calculating the spindle width as a function of the spindle length. Furthermore, we proposed a possible force-balance model based on this equation for setting the spindle width.
[1] Hara Y., Kimura A. Curr. Biol. 19, 1549-1554 (2009)

3538-Pos Board B399
Intracellular Spatial Localization Regulated by the Microtubule Network
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The commonly recognized mechanisms for spatial regulation inside the cell are membrane-bounded compartmentalization and biochemical association with subcellular organelles. We use computational modeling to investigate another spatial regulation mechanism mediated by the microtubule network in the cell. Our results demonstrate that the mitotic spindle can impose strong sequestration and concentration effects on molecules with binding affinity for microtubules, especially dynein-directed cargoes. The model can recapitulate the essence of three experimental observations on distinct microtubule network morphologies: the sequestration of germ plasm components by the mitotic spindles in the Drosophila syncytial embryo, the asymmetric cell division initiated by the time delay in centrosome maturation in the Drosophila neuroblast, and the diffusional block between neighboring nuclei in the Drosophila syncytial embryo. Our model thus suggests that cell cycle-dependent change in the microtubule network is critical for achieving different spatial regulation effects; that is, the microtubule network provides a spatially extensive docking platform for molecules and gives rise to a ''structured cytoplasm'', in contrast to a free and fluid environment.

3539-Pos Board B400
Simulating Self-Organization of Microtubules Interacting with Motor Protein-Coated Beads in Microscopic Chambers
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Spatial organizations of microtubules play important roles in cell morphologies and spatial order of cell organelles. In cells, microtubules are self-organized into patterns through interactions with various associated proteins, including motor proteins, and microtubule organizing centers. Self-organized patterns of microtubules generated by multimeric motor protein complexes have been reconstituted in vitro, and extensively studied. In addition to interactions with motor proteins, spatial constraints, such as cell membranes, are considered to play some roles in the pattern formations. However, studies on the roles of spatial constraints are limited. Here, we have simulated pattern formations of microtubules interacting with motor protein-coated beads in chambers of micrometer scale. To simulate microtubule movements, we modeled a microtubule as the Kramers chain of a linear polymer, and performed Brownian dynamics simulations. The simulations showed that dynamic patterns of microtubules were formed in chambers of various shapes, such as thin square and hexagonal prisms. Relative importance among geometries of microscopic chambers, microtubule properties, and motor protein properties will be discussed.

3540-Pos Board B401
Biomolecular Motors and Switches: From Machines to Drugs
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Molecular motors and molecular switches lie at the heart of key biological processes, from the division and growth of cells to the muscular movement of organisms. They represent attractive targets for drug design, as their aberrant function is associated with many diseases including cancer, diabetes and neurodegenerative disorders. To understand how these fascinating nanomachines function, and how their disfunction is related to disease, requires the consideration of multiple spatial and temporal scales as well as the successful integration of experiment, molecular simulation and theory. I have developed a state-of-the-art multi-level computational approach to investigate the structure, dynamics and interactions of prototypical motor and switch systems.
Our approach couples bioinformatics (to probe sequence-structure-function relationships); molecular dynamics (to investigate essential conformational changes); Brownian dynamics (for diffusional protein-protein and protein-ligand encounters); and computer-aided drug design (for discovering novel therapeutics). I will describe two discoveries that exemplify the power of this approach. First, how it uncovered the importance of electrostatics in the biased motion of kinesin motors along microtubules, and how this information enabled the rational design of mutant motors with tailored velocities. Second, how it revealed that the traditional ''induced fit'' view for activating conformational changes in molecular switches should be replaced by a ''conformational selection'' model, and how this framework led to the discovery of novel small molecule Ras inhibitors that represent new avenues for chemotherapeutic development.
Images and animations related to this work can be found at:
< http://mccammon.ucsd.edu/~bgrant/ >